Remarks

The Rejection of Claims 1, 2, 4, 6, 8-11, 13, 23, 24, 26, 28, 30-33, and 35 Under 35 U.S.C. § 103(a)

Claims 1, 2, 4, 6, 8-11, 13, 23, 24, 26, 28, 30-33, and 35 are rejected as unpatentable over Whitcombe *et al.* (WO 97/42345; "Whitcombe") in view of Lane *et al.* (U.S. Patent 6,165,714; "Lane"). The rejection is respectfully traversed.

Claims 1 and 23 are the independent claims of the rejected claim set. Claim 1 is directed to a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample. The method comprises four steps: (i) amplifying a region of DNA comprising a polymorphic locus in the sample; (ii) labeling the amplified DNA products; (iii) hybridizing the labeled amplified DNA products to a probe on a solid support; and (iv) detecting the hybridized labeled amplified DNA products. The amplification is carried out using a pair of primers. The first primer terminates at its 3' end at the polymorphic locus and terminates at its 5' end with a 5' portion that is identical in sequence to all or part of a probe on a solid support and not complementary to the region of DNA. The step of amplifying produces a first strand and a second strand. The first strand comprises a portion identical to all or part of the probe, and the second strand comprises a 5' portion complementary to all or part of the probe.

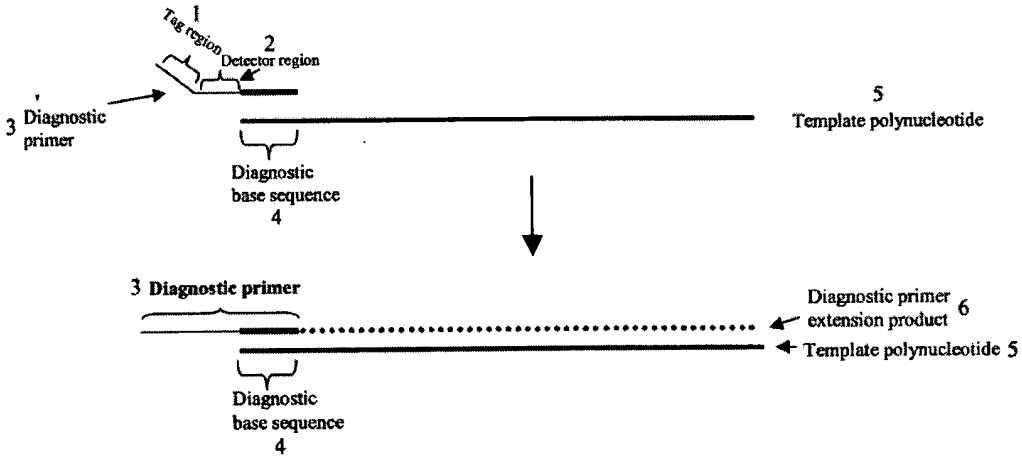
Claim 23 is directed to a method to prepare samples for analysis to determine a nucleotide at a polymorphic locus in a nucleic acid sample. The method recites the steps of amplifying, labeling, and hybridizing as in claim 1, but does not recite the step of detecting.

The Patent Office bears the initial burden of proving that a claimed invention is obvious. To make this *prima facie* showing three criteria must be met:

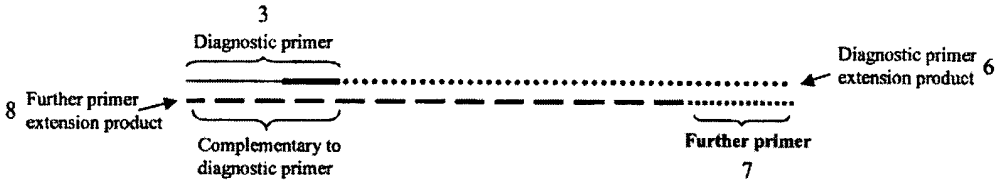
> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP § 1243. The rejection fails to meet the first criterion, *i.e.*, there is no suggestion or motivation to combine the teachings of Whitcombe and Lane to arrive at the claimed invention. The prior art references must also be considered in their entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983).

Whitcombe teaches methods for detecting a target nucleic acid sequence in a sample of polynucleotides. The methods employ primers and polymerization of nucleotides. A tailed diagnostic primer (3) is hybridized to a diagnostic base sequence (4) and extended on a template polynucleotide (5) to produce a diagnostic primer extension product (6). The tail of the diagnostic primer comprises a tag region (1) and a detector region (2). (Page 2, lines 1-6.)

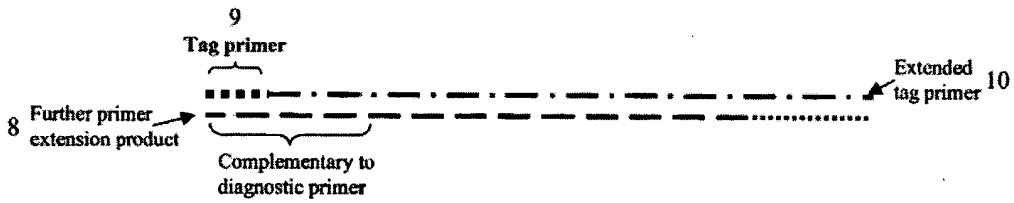


A further primer (7) is hybridized to the diagnostic primer extension product (6) and extended to produce a further primer extension product (8). (Page 2, lines 6-7.)



The sequence complementary to the detector region of the diagnostic primer in the further extension product (8) can be detected. "The detector region in the further extension product may be detected." (Page 2, lines 11-12.) Whitcombe teaches detection is via a probe on a solid support as one of many possible modes. (Page 3, lines 1-2.)

Whitcombe teaches additional steps that can optionally be performed. A tag primer (9) can be hybridized to the further primer extension product (8) at the sequence complementary to the tag region of the diagnostic primer and extended (Page 2, lines 7-9.)



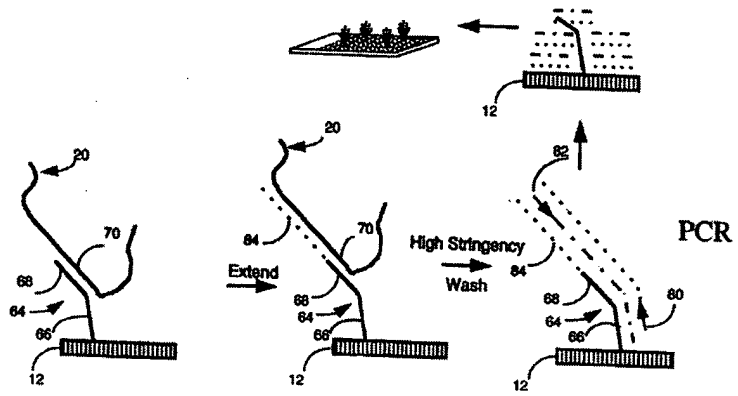
This product (the extended tag primer; 10) can be amplified using the tag primer (9) and the further primer (7). (Page 4, lines 5-6.)

None of the primers disclosed by Whitcomb (the diagnostic (3), the further (7), or the tag (9) primer) "terminates at its 5' end with a 5' portion which is identical in sequence to all or part of a probe on a solid support" as recited in claims 1 and 23. The Office Action acknowledges that Whitcomb lacks this teaching. (Paper 0603, page 3, lines 19-20.) Lane is cited by the Office Action as supplying this missing element. The Office Action asserts that Lane teaches "a

similar method wherein a region of DNA is amplified using a primer pair wherein the first primer terminates that the 5' end with a portion which is identical to the probe on the solid support." (Paper 0608, page 3, lines 20-22.)

Lane teaches methods for detecting a target nucleotide sequence in a nucleic acid sample. (Column 1, lines 31-33.)

Fig. 9B



A nucleic acid sample is applied to an array of probes on a solid support (12). The probes (64) comprise a 3' sequence (68) that is complementary to the target nucleotide sequence (70). The probes hybridize to the target nucleotide sequence via the 3' sequence (68). A diffusion-limiting matrix is applied to the solid support. The target nucleotide sequence hybridized to the probe is amplified. The amplification products form localized foci on the solid support (represented as bushes in top center panel) because the diffusion-limiting matrix prevents the diffusion of the amplification products from the site where the target nucleic acid hybridized to the probe. The foci are detected. (Column 3, lines 48-65.)

In a specific embodiment of the invention Lane teaches that the probe (64) hybridized to the target nucleotide sequence (70) is extended (84) in a single strand extension reaction. (Figure

9B; Column 8, lines 29-31.) A pair of primers (80 & 82), one of which (80) is identical to a portion of the probe, is used to amplify the extended probe (64 & 84). (Figure 9B; Column 8, lines 37-38.) The amplification products form diffusion-limited foci (represented as bushes in top center panel) which are then detected. (Figure 9B; Column 8, line 41.)

Lane does not teach or suggest an amplification primer that "terminates at its 3' end at a polymorphic locus" and that "terminates at its 5' end with a 5' portion which is identical in sequence to all or part of a probe on a solid support." Lane only teaches a primer that comprises a 5' portion that is identical to a probe on a solid support.

The Office Action asserts that one of ordinary skill in the art would have been motivated to modify the primer taught by Whitcombe (which contains a 5'-most portion identical to a tag sequence, a middle portion identical to a detector region, and a 3'-most portion complementary to a target nucleic acid) with the primer taught by Lane (which comprises a 5' portion identical to a probe) to arrive at the first primer recited in the claimed method, which "comprises a 3' portion which is complementary to the region of DNA" and "terminates at its 5' end with a 5' portion which is identical in sequence to all or part of a probe on a solid support." The Office Action asserts that one of ordinary skill in the art would have been motivated to modify the diagnostic primer taught by Whitcombe with the teachings of Lane "to thereby simplify primer design by elimination of the tag sequence." (Paper 0603, page 3, line 26 to page 4, line 1.) Whitcombe, however, teaches several advantages to having a tag region present at the 5'-terminal end of the diagnostic primer. Such advantages would lead one of ordinary skill in the art away from simplifying the primer design by eliminating the advantageous region. Whitcombe teaches that the 5' terminal tag region of the diagnostic primer reduces artifacts

introduced during amplification reactions. "Thus whilst primer dimers and other inter-primer artifacts could occur during first phase diagnostic priming, these cannot be amplified during subsequent rounds of tag specific priming." (Page 4, lines 25-27, emphasis added.) Whitcombe also teaches that the 5' terminal tag region reduces reagent costs because different diagnostic primers, which anneal to different diagnostic base sequences, can be designed to contain the same tag region. "The use of a common tag primer and common tail sequences has significant cost advantages for a typical assay." (Page 3, lines 24-25.) Thus all the different diagnostic base sequences can be amplified with a single tag primer in a single subsequent reaction. Further, Whitcombe teaches that if multiple diagnostic base sequences are amplified in a single reaction using a single tag primer, the amplification efficiencies of each of the different templates are more equal than if multiple sets of primers are used to amplify the different templates. "We have found that the use of identical tag sequence can be advantageously used to even out the efficiencies of different amplification reactions." (Page 4, lines 11-12.) Thus Whitcombe teaches that having a 5' tag region (not identical to a probe on a solid support) of a diagnostic primer (i) reduces amplification artifacts, (ii) reduces costs of amplification reactions, and (iii) reduces uneven amplification in reactions of more than one product. These disclosed advantages would have taught away from eliminating the tag region. Thus, one of ordinary skill in the art would not have been motivated to eliminate the 5'-terminal tag region of the diagnostic primer to simplify primer design.

Lane also does not provide any motivation to modify Whitcombe's diagnostic primer to eliminate its tag portion. The Office Action asserts, however, that Lane provides such a teaching. The Office Action asserts that

> Lane et al teach that the extension product is detected upon capture (Column 8, lines 23-41). Therefore, the tag sequence of Whitcombe et al is not required for extension product detection. Hence one of ordinary skill in the art would have been motivated to eliminate the tag sequence of the Whitcombe et al primer based on the teaching of Lane et al wherein the tag sequence is not required for product detection.

Paper 0603, page 4, lines 1-5. Lane, however, does not teach detection of extension products upon capture. Lane teaches hybridization of a target nucleic acid to a probe on a solid support and subsequent extension of the probe. Thus, the probe extension product is not captured because it is already bound to the solid support. The target nucleic acid is captured and then extended. Furthermore, Lane does not detect the extension products. Lane teaches amplification of the probe extension products and detection of the amplification products. Thus, Lane simply does not supply a teaching that extension products are detected upon capture on probes, as asserted in the Office Action. Therefore, Lane does not supply the motivation asserted in the Office Action to combine Whitcombe and Lane to arrive at the claimed primer that "terminates at its 5' end with a 5' portion which is identical in sequence to all or part of a probe on a solid support."[1]

The Office Action has failed to identify any teaching of Whitcombe or Lane that would motivate or suggest to one of ordinary skill in the art to modify Whitcombe's diagnostic primer to eliminate the tag sequence and arrive at the first primer recited in the claimed methods.

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[1] The Office Action may have intended that "the extension product detected upon capture" refer to the products resulting from amplification of the probe extension products and associated with the probe extension products via a diffusion-limiting matrix. See Lane Fig. 9B, top left panel. One of ordinary skill in the art would not have combined this teaching of Lane with the teachings of Whitcombe to arrive at the claimed first primer that "terminates at its 5' end with a 5' portion which is identical in sequence to all or part of a probe on a solid support." Whitcombe teaches several advantages of retaining a 5' terminal tag region in his primer (as discussed above). Moreover, the methods taught by Lane and Whitcombe are so different that they do not lend themselves to combination (as discussed below).

Neither Whitcombe nor Lane provide any teaching that would motivate one of ordinary skill in the art to modify the diagnostic primer taught by Whitcombe to arrive at the first primer that "terminates at its 5' end with a 5' portion which is identical in sequence to all or part of a probe on a solid support." To the contrary, Whitcombe teaches away from such a modification.

Moreover, considered as a whole, one of ordinary skill in the art would not have looked to Lane to modify Whitcombe because the teachings of Whitcombe and Lane are directed to two completely different methods of detecting target DNA.

- Whitcombe and Lane amplify target nucleic acids in different phases that comprise different states of matter. Whitcombe amplifies a template polynucleotide in solution. Lane amplifies a target nucleic acid tethered to a solid support.
- Whitcombe and Lane teach different means of attachment of the labeled, amplified, target nucleic acids to the solid support. Whitcombe hybridizes the amplification products to probes on a solid support. Lane localizes the amplification products with the solid support via a diffusion-limiting matrix.
- Whitcombe and Lane teach that different nucleotide sequences in the target nucleic acid hybridize to the probe on the solid support. Whitcombe teaches that a diagnostic primer extension product hybridizes to the probe on the solid support via a detector region that is artificially introduced by the diagnostic primer during amplification. Lane teaches that the target nucleic acid hybridizes to the probe on the solid support via a sequence naturally present in the target nucleic acid.
- Whitcombe and Lane perform their method steps in a completely different order. Whitcombe teaches that first a *target nucleic acid is amplified*, and then the amplified

target nucleic acids are hybridized to a probe on a solid support for detection. Lane teaches that first the *target nucleotide is hybridized to a probe* on a solid support and then the *probe is extended* on the target nucleotide so that the extended probe can be amplified and detected.

Thus, the methods taught by Whitcombe and Lane, considered as a whole, are so distinct that their combination would not suggest itself to the person of ordinary skill in the art. Moreover, as demonstrated above, there is no teaching in Whitcombe or Lane suggests the desirability of combining their teachings to arrive at a primer that "terminates at its 5' end with a 5' portion which is identical in sequence to all or part of a probe on a solid support." Thus, the rejection fails to meet the requirement that there be some suggestion or motivation to combine Whitcombe and Lane to arrive at the claimed invention. The *prima facie* case of obviousness must fail. Applicants respectfully request withdrawal of this rejection to claims 1 and 23.

If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988). Thus, the rejection of dependent claims 2, 4, 6, 8-11, 13, 24, 26, 28, 30-33, and 35 should also be withdrawn.

The Rejection of Claims 3 and 25 Under 35 U.S.C. § 103(a)

Claims 3 and 25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Whitcombe in view of Lane and further in view of Hames *et al.* (Nucleic Acid Hybridization: a practical approach, 1998, pp. 35, 36, and 42-44; "Hames"). Applicants respectfully traverse.

Claims 3 and 25 are dependent on claims 1 and 23, respectively, and further recite that terminal transferase catalyzes the step of labeling. The Office Action concedes that Whitcombe

and Lane do not teach the use of terminal transferase for labeling as recited in claims 3 and 25. (Paper 0603, page 9, lines 1-2.) Hames is cited as teaching the use of terminal transferase to label the 3' end of DNA molecules with a single radiolabeled nucleotide. (Paper 0603, page 9, lines 2-3.)

However, as discussed above, there would have been no motivation to combine the teachings of Whitcombe with those of Lane to arrive at a primer that "terminates at its 5' end with a 5' portion which is identical to a portion of a probe on a solid support" as required by the subject claims. Hamès merely teaches scientific protocols that are used to perform terminal transferase reactions. Thus Hames does not contribute any teaching that would motivate one of ordinary skill in the art to modify Whitcombe with Lane to arrive at a primer that "terminates at its 5' end with a 5' portion which is identical in sequence to all or part of a probe." Thus the combination of Whitcombe, Lane, and Hames does not render claims 1 and 23 obvious. Because the combination of Whitcombe, Lane, and Hames does not render claims 1 and 23 obvious, it does not render dependent claims 3 and 25 obvious. Withdrawal of this rejection to claims 3 and 25 is respectfully requested.

The Rejection of Claims 5, 14-16, 27, and 36-38 Under 35 U.S.C. § 103(a)

Claims 5, 14-16, 27, and 36-38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Whitcombe in view of Lane, and further in view of Harris *et al.* (WO 94/02634; "Harris"). Applicants respectfully traverse.

Claims 5, 14-16, 27, and 36-38 are dependent on claims 1 and 23, and further recite that the nucleotide is radioactively labeled (claims 5 and 27), or that the solid support is beads

(claims 14 and 36), a microtiter dish (claims 15 and 37), or a high-density array (claims 16 and 38).

The Office Action concedes that the combination of Whitcombe and Lane does not teach radioactively labeling nucleotides (paper 0603, page 10, lines 8-9) or that the solid support is beads, a microtiter dish, or a high-density array (paper 0603, page 11, lines 6-7). Harris is cited for teaching radioactively labeling nucleotides (paper 0603, page 10, lines 9-10) and a solid support that is a bead, microtiter dish, or high-density array (paper 0603 page 11, lines 7-11).

As discussed above, there would have been no motivation to combine the teachings of Whitcombe with those of Lane to arrive at a primer that "terminates at its 5' end with a 5' portion which is identical to a portion of a probe on a solid support" as required by the subject claims. Harris does not provide this missing motivation.

Harris teaches a method of detecting amplified target nucleic acids. The target nucleic acids are amplified and a detector tag is introduced into the amplification product. The detector tag is a label that permits detection of the amplified product. (Page 6, line 17 to page 7, line 1; See also page 35, line 8 through page 36, line 13.) A probe, which is attached to a solid support, detects the labeled amplification products. The amplification primers that are used in Harris' method do not contain any sequence that is identical to a probe. Harris teaches that the probes hybridize to a sequence in the amplified target nucleic acids that is distant from the annealing site of the amplification primers. "Preferably, the capture probe hybridizes to a central section of the amplified nucleic acid sequence – away from any primer or primer complementary nucleic acid sequences." (Page 8, lines 7-9.) Thus these amplification primers do not contain any sequence identical to a probe. Harris alternatively teaches that the probes hybridize to the amplification

primers, *i.e.*, the primers are complementary to the probe. "[F]or methods where the amplified product is formed only from the primers (e.g. Ligase Chain Reaction, LCR), then the product target sequence [probe hybridization site] will be in part of one strand of two joined primers and will span across the joining point." (Page 14, lines 10-14.) Thus, these amplification primers comprise a sequence that is *complementary* to the probe. Harris teaches amplification primers that do not contain any sequence that is identical to a probe and thus contributes no motivation to modify Whitcombe with Lane to arrive at a primer that "terminates at its 5' end with a 5' portion which is identical in sequence to all part of a probe."

One of ordinary skill in the art would not have been motivated to combine Whitcombe, Lane, and Harris to arrive at a primer that "terminates at its 5' end with a 5' portion which is identical in sequence to all or part of a probe." Thus the combination of Whitcombe, Lane, and Harris fails to render claims 1 and 23 obvious. The obviousness rejection against dependent claims 5, 14-16, 27, and 36-38 must also fail. Applicants respectfully request the withdrawal of this rejection to claims 5, 14-16, 27, and 36-38.

The Rejection of Claims 7 and 29 Under 35 U.S.C. § 103(a)

Claims 7 and 29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Whitcombe in view Lane and further in view of Vary *et al.* (U.S. Patent 4,851,331; "Vary"). Applicants respectfully traverse.

Claims 7 and 29 are dependent on claims 1 and 23, and further recite that the nucleotide is epitopically labeled. The Office Action concedes that the combination of Whitcombe and

Lane does not teach epitope labeling of nucleotides. (Paper 0603, page 12, line 22.) Vary is cited as providing this teaching. (Paper 0603, page 13, lines 16-19.)

As discussed above, there would have been no motivation to combine the teachings of Whitcombe with those of Lane to arrive at a primer that "terminates at its 5' end with a 5' portion which is identical to a portion of a probe on a solid support" as required by the subject claims. Vary does not provide this missing motivation.

Vary teaches a method of detecting a target nucleotide sequence in the nucleic acids of a biological sample. The nucleic acids of the sample are contacted with a probe polynucleotide which anneals to a target nucleotide sequence. The probe polynucleotide is extended using labeled nucleotides and is detected. (Column 1, line 57 through column 2, lines 3-6.) Vary also teaches that the probe polynucleotide can be extended on an immobilized support. (Column 4, lines 14-17.) If extension occurs on an immobilized support, the probe polynucleotide comprises a 3' sequence complementary to the target nucleotide sequence and a 5' sequence complementary to a binding segment present in an immobilized polynucleotide attached to a support. (Column 7, lines 23-49; Figure 3.) Thus Vary teaches that a primer, *i.e.*, probe polynucleotide, has a 3' sequence that is complementary to a target polynucleotide and a 5' sequence that is *complementary* to a polynucleotide attached to a solid support. Thus, Vary provides no motivation to combine the teachings of Whitcombe with Lane to arrive at a primer that "terminates at its 5' end with a 5' portion which is *identical in sequence* to all or part of a probe on a solid support." At most, Vary teaches a primer that terminates at its 5' end with a 5' portion that is *complementary* to a probe.

One of ordinary skill in the art would not have been motivated to combine Whitcombe, Lane, and Vary to arrive at a primer that "terminates at its 5' end with a 5' portion which is identical in sequence to all or part of a probe." The combination of Whitcombe, Lane, and Vary does not teach or suggest all the elements recited in claims 1 and 23. Thus the obviousness rejection against claims 7 and 29 must also fail. Withdrawal of this rejection to claims 7 and 29 is respectfully requested.

The Rejection of Claims 12 and 34 Under 35 U.S.C. § 103(a)

Claims 12 and 34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Whitcombe in view of Lane and further in view of Brown *et al.* (U.S. Patent 5,807,522; "Brown"). Applicants respectfully traverse.

Claims 12 and 34 are dependent on claims 1 and 23, and further recite that the sample comprises DNA from two or more individuals. The Office Action concedes that the combination of Whitcombe and Lane does not teach a sample comprising DNA from two or more individuals. (Paper 0603, page 14, lines 23-24.) Brown is cited as providing this teaching. (Paper 0603, page 14, lines 24-26.)

As discussed above, there would have been no motivation to combine the teachings of Whitcombe with those of Lane to arrive at a primer that "terminates at its 5' end with a 5' portion which is identical to a portion of a probe on a solid support" as required by the subject claims. Brown does not provide this missing motivation.

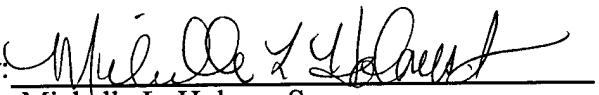
Brown teaches the use of microarrays to examine an *S. cerevisiae* chromosomal library. (Example 1, column 16, line 3, to column 17, line 40.) *S. cerevisiae* chromosomal DNA was

amplified and hybridized to an array of probes. The primers used to amplify the *S. cerevisiae* chromosomal DNA had a random nucleotide sequence; the *S. cerevisiae* DNA was "randomly amplified." (Column 16, lines 45-46.) The probes to which the amplified *S. cerevisiae* DNA was hybridized "were randomly amplified PCR products using physically mapped lambda clones of *S. cerevisiae* genomic DNA as templates." (Column 16, lines 10-13, citations omitted.) Thus the probes have a sequence that is *complementary* to the primer and yeast chromosomal DNA.

Thus Brown does not contribute any teaching that would motivate one of ordinary skill in the art to modify Whitcombe with Lane to arrive at a primer that "terminates at its 5' end with a 5' portion which is *identical in sequence* to all or part of a probe." Thus the combination of Whitcombe, Lane, and Brown does not render claims 1 and 23 obvious. Because the combination of Whitcombe, Lane, and Brown does not render claims 1 and 23 obvious, it does not render dependent claims 12 and 34 obvious. Withdrawal of this rejection to claims 12 and 34 is respectfully requested.

Respectfully submitted,

Date: September 25, 2003

By: 

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